surround the interface between the multicentre committee and local committees—both in terms of time and individual idiosyncrasy.

So what can be done? Holley and Foster found generally high standards of practice in 27 local research ethics committees in the South Thames region, and there is little reason to suspect that the situation is different elsewhere.[6] They concluded that the problems researchers have with multicentre research are structural and logistic, and not due to substandard working of local research ethics committees.[7] They also noted a steady improvement over time.

Some relatively simple measures would help solve the problem. Ah-See et al noted just two years ago that 15 out of 19 local research ethics committees approached had unique application forms.[8] Surely a single form with a small number of variants should be used nationwide.[8 9] Certainly a common form for multicentre research ethics committees is essential. A short form containing locally relevant information could be devised and sent electronically to local ethics committees, avoiding the need to send vast piles of papers.

There remains the problem of different modes of working and standards, which are occasionally highly idiosyncratic, between different local research ethics committees. A national advisory body is clearly needed to communicate regularly with all local committees, organise training programmes, and lay down clear guidance that is updated regularly. In return, local committees need better support, and their members need reasonable payment for what is often an onerous task. The guidance on handling multicentre proposals needs major reinforcement.

Research ethics committes have two major functions. On the one hand, they must protect patients and the public against harm from research—and against useless studies, which are unethical. They perform this function well, although at times in irritatingly nitpicking detail. On the other hand, they should encourage research that will in the long run improve health care and health. Here the system is still too obstructive. So have multicentre research ethics committees worked? The answer must be a qualified yes, but further improvement is needed if we are to continue to perform timely and valuable multicentre research in the United Kingdom.

K G M M Alberti *president*

Royal College of Physicians, Regent's Park, London NW1 4LE

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Risk of torsades de pointes with non-cardiac drugs

Doctors need to be aware that many drugs can cause QT prolongation

Many antiarrhythmic drugs are known to prolong ventricular repolarisation and provoke torsades de pointes. Recently, an increasing number of non-cardiac drugs have also been reported to have the same effects. These drugs share the same ability to block the rapid component of the delayed rectifier potassium channel (IKr), resulting in inhomogeneous lengthening of action potential, T wave abnormality, and QT interval prolongation. Depolarisation current at the tail of a prolonged action potential induces early after depolarisations, which in the setting of inhomogeneous ventricular recovery provokes torsades de pointes. Many doctors are unaware of the proarrhythmic risk associated with some non-cardiac drugs. With few exceptions, most papers published in scientific journals are anecdotal case reports. Notifications to regulatory authorities, the World Health Organisation, and pharmaceutical companies thus constitute much of the evidence base.

Two non-sedating antihistamines, terfenadine and astemizole, attracted regulatory attention in the early 1990s and have since been restricted to prescription only in the United Kingdom because of their unexpected association with QT prolongation, torsades de pointes, and sudden death.[1 2] The adverse effects of terfenadine appeared to depend on concentration, occurring at supraclinical doses or at normal doses in patients also taking drugs that inhibit cytochrome P-450 drug metabolism—such as imidazole antifungals and some macrolide antibiotics—and in patients with congenital long QT syndrome.[2]

The cardiac safety of newer non-sedating antihistamines (ebastine, loratadine, cetirizine, acrivastine, fexofenadine, and mizolastine) will require confirmation but some and not others block IKr and might well provoke clinical arrhythmia. Although the absolute incidence of cardiotoxicity with antihistamines is very low,[3] the likelihood of causing cardiac arrhythmia must be assessed carefully because these drugs are liberally prescribed for self limiting, non-fatal diseases.

Some antibiotics (such as macrolides and fluoroquinolones), antimalarials, and imidazole antifungal

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agents can cause QT prolongation and torsades de pointes.[4–7] Torsades de pointes is rare, however, and has not occurred with all antimicrobials that prolong the QT interval. Intravenous erythromycin prolongs the QT interval, causes dispersion of recovery across the ventricular wall, and occasionally induces torsades de pointes.[4] In the case of the fluoroquinolones, sparfloxacin and grepafloxacin (now withdrawn in most countries) lengthen the QT interval, whereas levofloxacin and ofloxacin apparently do not. Quinine prolongs the QT interval at standard doses,[5] as does halofantrine, particularly when it is combined with mefloquine.[6] Ketoconazole prolongs the QT interval by directly blocking IKr and by delaying the cytochrome P-450 dependent metabolism of other drugs that also prolong the QT interval.[7]

Tricyclic antidepressants are particularly cardiotoxic. Amitriptyline, doxepin, desipramine, imipramine, and clomipramine have all been associated with QT prolongation,[8 9] and sudden death has been reported with desipramine, clomipramine, or imipramine.[9] Although there is an unexplained incidence of sudden death in schizophrenic patients, neuroleptics themselves are associated with sudden death, and many cause QT prolongation and torsades de pointes at therapeutic or toxic doses. Haloperidol, chlorpromazine, trifluoperazine, pericycline, prochlorperazine, and fluphenazine are incriminated, but thioridazine may be the worst.[10]

There is disagreement about the cardiac safety of sertindole, a relatively new neuroleptic agent. Despite the 27 deaths (16 cardiac events) associated with its use among 2194 patients who participated in premarketing clinical trials, an independent review found that no causal relation could be established between sertindole and these deaths.[11] In a recent update, however, the Committee on Safety of Medicines described reports of 36 deaths (including some sudden cardiac deaths) and 13 serious but non-fatal arrhythmias associated with sertindole.[12] As a result, the manufacturer has voluntarily suspended its use pending a full evaluation of risks and benefits.

Pimozide, another antipsychotic, is well known to cause QT prolongation and torsades de pointes. Forty reports (16 deaths) of serious cardiac reactions (predominantly arrhythmias) with pimozide use were reported to the Committee on Safety of Medicines from 1971 to 1995.[13]

Cisapride has attracted much recent attention because of reports of QT prolongation and torsades de pointes.[14] Among the 34 cases of torsades de pointes and 23 cases of QT prolongation associated with cisapride reported to the Food and Drug Administration from 1993 to 1996 were four deaths and 16 resuscitated cardiac arrests.[14] Many of the patients were also taking imidazole or a macrolide antibiotic, which could inhibit the P-450 CYP3A4 isoenzyme responsible for cisapride metabolism.

Other conditions that are likely to increase the degree of QT prolongation from drugs include organic heart disease, particularly congestive heart failure; metabolic abnormalities (such as hypokalaemia and hypomagnesaemia); and sinus bradycardia or heart block. Women are also more susceptible.

In clinical practice, adverse effects of QT prolonging drugs can be prevented by not exceeding the recommended dose; by restricting the dose in patients with pre-existing heart disease or other risk factors; and by avoiding concomitant administration of drugs that inhibit drug metabolism or excretion, prolong the QT interval, or produce hypokalaemia. The potassium concentration should be checked regularly and potassium sparing diuretics should be preferred.

If the patient develops torsades de pointes the offending drug should be stopped and electrolyte abnormalities corrected. When prescribing a QT prolonging drug, it is helpful to give the patient a warning card listing risk factors (including other drugs that prolong QT), precautions, and contraindications for coprescriptions. Although not currently implemented, we would like to recommend that drugs that prolong QT should be listed and regularly updated in a national drug catalogue (such as the *British National Formulary*). Any adverse event suggestive of cardiac arrhythmias should be urgently reported to drug safety authorities and drug manufacturers.

The number of non-cardiac drugs that expose patients to a significant risk of potentially lethal arrhythmias through causing QT prolongation and torsades de pointes is large. All doctors, and patients who receive these drugs, should be aware of this risk and take the precautions to minimise proarrhythmia.

Yee Guan Yap *British Heart Foundation research fellow*
John Camm *professor of cardiology and head*

Department of Cardiological Sciences, St George's Hospital Medical School, London SW17 0RE (jcamm@sghms.ac.uk)

JC acts as a consultant for Pfizer, Astra Zeneca, GlaxoWellcome, Synthelabo, Ludbeck, and Grunethal.

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